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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte ALAN DAVID WATSON, MICHAEL WENDLAND, PER JYNGE, JAN OLOF KARLSSON, HEIDI BRUROK, PAL RONGVED, and MAYTHEM SAEED

Appeal 2008-0142
Application 09/975,317
Technology Center 1600

Decided: June 19, 2008

Before ERIC GRIMES, RICHARD M. LEBOVITZ, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal from the final rejection of claims 76-81, 84-86, 88-93, and 96. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

The claims are directed to a method of distinguishing viable myocardial tissue from necrotic (infarcted tissue) comprising administering a manganese chelate complex of a formula I comprising subjecting the tissue to magnetic resonance imaging (MRI).

According to the Specification, manganese chelates have been suggested in the prior art for myocardial imaging (Spec. 2-3). The Specification states that the inventors "surprisingly" found "that substantially lower, clinically acceptable, dosages of manganese may be used in fast or ultra-fast imaging techniques to provide an effective method of myocardial imaging, in particular to provide important information about myocardial viability during or following a severe heart attack or coronary occlusion" (Spec. 3-4).

Claims 76-81, 84-86, 88-93, and 96 are on appeal (App. Br. 2). Appellants appeal from the Final Rejection of:

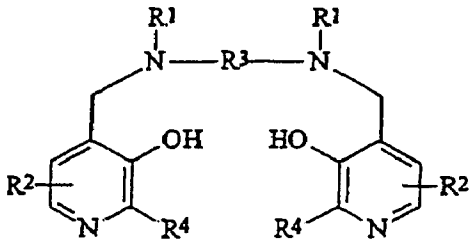
1) Claims 76, 77, 79-81, 84-86, 88-93, and 96 under 35 U.S.C. § 103(a) as obvious over Rocklage '744 (U.S. Pat. No. 5,190,744, Mar. 2, 1993) in view of Rocklage '931 (U.S. Pat. No. 4,889,931, Dec. 26, 1989) (Ans. 3); and

2) Claims 77, 78, and 96 under 35 U.S.C. § 103(a) as obvious over Rocklage '744 in view of Goldenberg (U.S. Pat. No. 5,632,968, May 27, 1997) (Ans. 7).

Claims 96, 77, and 78 are representative and read as follows:

96. A method of distinguishing viable myocardial tissue from necrotic (infarcted) tissue in a human or nonhuman body, said method comprising administering to said body a physiologically acceptable manganese complex

wherein said manganese complex is a manganese chelate complex having a K_a value of from 10^7 to 10^{25} and a formula I:



; (I)

or a salt thereof

(wherein in formula I

each R^1 independently represents hydrogen or $-CH_2COR^5$;

R^5 represents hydroxy, optionally hydroxylated alkoxy, amino or alkylamido;

each R^2 independently represents a group XYR^6;

X represents a bond, or a C_{1-3} alkylene or oxoalkylene group optionally substituted by a group R^7;

Y represents a bond, an oxygen atom or a group NR^6;

R^6 is a hydrogen atom, a group $COOR^8$, an alkyl, alkenyl, cycloalkyl, aryl or aralkyl group optionally substituted by one or more groups selected from $COOR^8$, $CONR^8_2$, NR^8_2, OR^8, $=NR^8$, =O, $OP(O)(OR^8)$ R^7 and OSO_3M;

R^7 is hydroxy, an optionally hydroxylated, optionally alkoxylated alkyl or aminoalkyl group;

R^8 is a hydrogen atom or an optionally hydroxylated, optionally alkoxylated alkyl group;

M is a hydrogen atom or one equivalent of a physiologically tolerable cation;

R^3 represents a C_{1-8} alkylene group, a 1,2-cycloalkylene group, or a 1,2-arylene group; and

each R^4 independently represents hydrogen or C_{1-3}, alkyl);

at a dosage of 0.001 to 0.2 mmol/kg bodyweight, within a period of from 3 to 6 hours following administration of said complex or salt thereof subjecting said body to a magnetic resonance imaging procedure capable of generating images with time intervals of less than 0.5 seconds and thereafter providing a series of images of the myocardium of said body and distinguishing viable myocardial tissue from infarcted tissue;

with the proviso that said manganese complex or salt thereof is the only contrast agent administered in said method.

77. A method as claimed in claim 96 wherein said imaging procedure is a gradient echo or echo planar imaging procedure.

78. A method as claimed in claim 77 wherein said imaging procedure is an inversion recovery echo planar imaging procedure.

OBVIOUSNESS OVER ROCKLAGE '744 AND ROCKLAGE '931

Claims 76, 77, 79-81, 84-86, 88-93, and 96 stand rejected under 35 U.S.C. § 103(a) as obvious over Rocklage '744 in view of Rocklage '931.

Scope and content of the prior art

In making an obviousness determination, the Examiner must first identity the scope and content of the prior art. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Thus, we first turn to the prior art. The following numbered findings of facts ("FF") summarize the prior art relied upon by the Examiner in setting forth the basis of the rejection.

The Rocklage '744 patent

1. Rocklage '744 describes the use of MRI for detecting blood flow variations "particularly useful in the determination of the extent and severity of ischemia" (Rocklage '744, at col. 1, ll. 10-12).

2. To accomplish the method, a contrast enhancing amount of paramagnetic metal is administered to the cardiovascular system (Rocklage '744, at col. 1, ll. 55-65).

3. The method can be carried out using a fast or ultra fast imaging technique "capable of generating images with time intervals of less than 5 seconds, especially less than 0.5 seconds and more especially less than 100 milliseconds" (Rocklage '744, at col. 2, ll. 10-18).

4. Manganese ("Mn") chelates are among a list of "[p]articularly suitable paramagnetic metal ions" for use as a contrast agent in Rocklage '744's method (at col. 4, ll. 50-55).

5. "For most MS contrast agents the appropriate dosage will generally lie in the range 0.02 to 3 mmol paramagnetic metal/kg bodyweight, especially 0.05 to 1.5 mmol/kg, particularly 0.08 to 0.5, and more especially 0.1 to 0.4 mmol/kg. It is well within the skill of the average practitioner in this field to determine the optimum dosage for any particular MS contrast agent by simple experiment, either in vivo or in vitro" (Rocklage '744, at col. 5, ll. 54-61).

6. In the examples, a cerebral artery ("MCA") of an adult cat was occluded to produce cerebral ischemia (Rocklage '744, at col. 7, ll. 26-32). After occlusion, a Dy contrast agent was administered (*id.* at col. 7, ll. 48-51).

7. Successive MRI images were obtained for up to 12 hours following occlusion (Rocklage '744, at col. 7, ll. 40-42). "Within 3-5 hours after MCA occlusion, . . . images also demonstrated tissue injury clearly" (*id.* at col. 9, ll. 14-16).

8. Rocklage '744 states that its method can be utilized in "identifying and providing an indication of the severity of cerebral or coronary ischemias or infarcts" and "has a broad range of possible diagnostic and evaluative applications" (Rocklage '744, at col. 2, ll. 33-37).

9. Rocklage '744 also states: "It seems likely that the method of the invention may be able to help identify reversibly ischemic penumbra from infarcted tissue based on the degree and duration of perfusion deficit to cerebral tissues" (Rocklage '744, at col. 10, ll. 3-6).

The Rocklage '931 patent

10. Rocklage '931 describes a contrast agent comprising a chelating agent chelated with a Mn ion of formula I (Rocklage '931, at col. 3, l. 34 to col. 4, l. 55; Ans. 3-4).

11. Mn chelates as contrast agents "are particularly useful as MRI contrast agents because manganese is less toxic than many paramagnetic metal ions" (Rocklage '931, at col. 1, ll. 13-16).

The Specification

12. "[S]everal proposals [in the prior art] have been made for the use of MnDPDP [a manganese chelate] in T_1-weighted spin echo imaging for detection of acute myocardial infarction" (Spec. 3).

Difference between the prior art and the claimed invention

Once the scope and content of the prior art have been determined, the next step is to identify the differences between the prior art and the claimed invention. *Graham*, 383 U.S. at 17. The following numbered findings of fact are pertinent to this issue:

13. Claim 96 is directed to a "method of distinguishing viable myocardial tissue from necrotic (infarcted) tissue in a human or nonhuman body."

14. The claimed method involves subjecting the body to an MRI procedure which is "capable of generating images with time intervals of less than 0.5 seconds."

15. A manganese complex is administered in the claimed method "having a K_a of from 10^7 to 10^{25} of formula I",

16. "at a dosage of 0.001 to 0.2 mmol/kg bodyweight", and

17. MRI is carried out "within a period of from 3 to 6 hours following administration" of the manganese complex.

18. Rocklage '744 describes an MRI imaging method that preferably generates time intervals "especially less than 0.5 seconds and more especially less than 100 milliseconds" (FF 3), meeting the limitation of claim 96 of "capable of generating images with time intervals of less than 0.5 seconds" (FF 14; Ans. 3).

19. A complex is administered by Rocklage '744 in its imaging method in an amount of "0.05 to 1.5 mmol/kg" (FF 5) which overlaps with the claimed range of "0.001 to 0.2 mmol/kg" (FF 16; Ans. 3).

20. Rocklage '744 also describes imaging within "3-5 hours after" administration of the contrast agent (FF 6, 7) – which overlaps with the claimed range of 3 to 6 hours (FF 17).

21. Rocklage '744 describes its method as useful for "identifying and providing an indication of the severity of . . . coronary ischemias or infarcts" (FF 8) and states that it "may be able to help identify reversibly ischemic penumbra from infarcted tissue based on the degree and duration of perfusion deficit to *cerebral* tissues" (FF 9), but does not expressly state that it is a "method of distinguishing viable *myocardial* tissue from necrotic (infarcted) tissue" as in claim 96 (FF 13) (emphasis added).

22. Mn contrast agents are described as useful by Rocklage '744 (FF 4), but Rocklage '744 does not describe the specific complex recited in claim 96 (Ans. 3).

23. However, Rocklage '931 describes a contrast agent comprising a chelating agent chelated with a Mn ion of formula I (FF 10) which is the same as the claimed formula I complex (FF 15; Ans. 3-4).

24. Appellants also admit in the Specification that Mn chelates had been proposed in the prior art for myocardial imaging (FF 12).

25. Since the claimed complex has the same formula as in Rocklage '931, it is reasonable to believe that it would also have the same K_a as in claim 96 (FF 15) since compounds of the same formula would be expected to have the same properties (Ans. 6).

Reason to combine the prior art

Once the differences between the prior art and the claimed invention have been ascertained, the next step is to identify a reason why persons of ordinary skill in the art would have been prompted to combine the prior art to have made the claimed invention. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). The following findings are relevant to this determination:

26. Rocklage '744 states that its method "may be able to help identify reversibly ischemic penumbra from infarcted tissue based on the degree and duration of perfusion deficit to cerebral tissues" (FF 9). In other words, the method can be used to distinguish "reversibly ischemic" or viable tissue from "infarcted" or necrotic tissue.

27. Thus, Rocklage '744's explicit goal is the same as in claim 96 (FF 13), but for "cerebral" tissue rather than "myocardial" tissue.

28. While Rocklage '744's stated goal (FF 9, 26) is in the context of cerebral tissues, Rocklage '744 also states that its method is applicable to "coronary . . . infarcts" (FF 8).

29. An "infarct" is defined as a "necrotic area of tissue resulting from failure of local blood supply."[1]

30. Since a coronary artery supplies blood to the heart (App. Br. 6), persons of ordinary skill in the art would have recognized that "coronary . . . infarcts" are a result of blockage to the coronary artery that lead to ischemia and subsequent necrosis in the heart, i.e., myocardial tissue.

31. Because Rocklage '744 states its method is applicable to coronary infarct, i.e., necrosis of heart tissue (FF 28) and "has a broad range of possible diagnostic and evaluative applications" (FF 8), Rocklage '744 would have reasonably suggested to persons of ordinary skill in the art that its method be used to distinguish "reversibly ischemic" or viable tissue from "infarcted" or necrotic tissue in the heart (FF 28, 29) as required by claim 96.

32. With regard to the specific Mn agent which is claimed, Rocklage '931 teaches a list of suitable contrast agents which would be expected to be equivalent for the purposes of MRI (FF 10; Ans. 7).

33. Persons of ordinary skill in the art would have had reason to have utilized the particular Mn contrast agent of Rocklage '931 for its low toxicity (FF 11) and would have expected it to work based on Rocklage '744's teaching that Mn is suitable for MRI imaging (Ans. 7).

34. It also admitted in the Specification that the prior art had suggested manganese chelates for myocardial imaging (FF 12), providing further reason to have utilized an Mn contrast agent of Rocklage '931.

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[1] The American Heritage Dictionary of the English Language, Houghton Mifflin Co., 673 (1976).

Analysis

The "examiner bears the initial burden, on review of the prior art . . , of presenting a *prima facie* case of unpatentability." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). In making an obviousness determination, a reason must be provided as to why persons of ordinary skill in the art would have combined the prior art to have arrived at the claimed invention. *See KSR*, 127 S. Ct. at 1741.

After reviewing the scope and content of the prior art and the reason for combining it, it is our opinion that prima facie obviousness of the subject matter of claim 1 has been established.

While there is no explicit statement in Rocklage '744 that its method could be used to distinguish between viable and necrotic *myocardial* tissue, the patent does make this statement for cerebral tissue (FF 9), describes the broad applicability of its method (FF 8), and specifically refers to coronary infarct (FF 8). From these teachings, we agree with the Examiner that Rocklage '744 reasonably suggests that its method could be utilized with success to distinguish between viable and necrotic myocardial tissue that would arise during a coronary infarct (FF 28-31) – a condition explicitly disclosed in Rocklage '744 (FF 8). We also agree that an ordinary artisan applying the method of Rocklage '744 would have found the Mn chelating agent in Rocklage '931 reasonably suggested for its expected advantages (lower toxicity) in MRI imaging (FF 11, 33). Appellants admit the manganese contrast agents had been proposed for myocardial imaging (FF 12, 34).

Appellants argue that Rocklage '744 describes its method for "cerebral or coronary ischemia and not myocardial ischemia" (App. Br. 5).

They assert that although

> Rocklage '744 also teaches that the same method would be useful in the detection of coronary ischemia, the myocardium and coronary arteries are different parts of the heart – the myocardium is the middle muscular layer of the heart wall, and coronary arteries surround the heart and branch out from the aorta to supply blood to the heart as would be appreciated by one of ordinary skill in the art. There is no motivation in Rocklage '744 which suggests the claimed invention nor is there a suggestion of the likelihood of success in arriving at the presently claimed invention.

(App. Br. 6).

This argument is not persuasive. First, Rocklage '744, in addition to coronary ischemia, also refers to coronary infarct which would have reasonably suggested application of its method to myocardial tissue that would be deprived of blood during a coronary infarct (FF 8, 29-31). Appellants have not addressed this specific disclosure of Rocklage '744.

Secondly, we disagree that there would be "no motivation . . . of the likelihood of success" to arrive "at the presently claimed invention" (App. Br. 6). As discussed above, Rocklage '744 teaches that its method can be used to distinguish necrotic from viable tissue, albeit cerebral tissue (FF 26). However, Rocklage '744 teaches that its method can be used to assess the severity of coronary infarct and describes it as having a broad range of diagnostic application (FF 8). Thus, Rocklage '744 does not express any reservations about the broad applicability of its method; consequently, persons of ordinary skill in the art would have reasonably expected that the method could be applied with success to other tissues, including myocardial tissue.

Appellants also argue that "Rocklage '744 can only be used to identify and/or monitor abnormal or modified blood flow. The method does not involve or allow for the detection of damaged tissue in accordance with the claims on appeal" (App. Br. 7). We do not agree. Rocklage '744 expressly states that its method "may be able to help identify reversibly ischemic penumbra from infarcted tissue based on the degree and duration of perfusion deficit to cerebral tissues" (FF 9). Rocklage '744 also states that its method is "particularly useful in the determination of the extent and severity of ischemia" (FF 1). Thus, Rocklage '744, in fact, teaches that its method can be used to assess damaged versus viable or "reversibly ischemic" tissues – the same purpose recited in claim 96.

Appellants state that the differential uptake of manganese by viable myocardial cells, but not "irreversibly damaged" myocardial cells is not suggested by the prior art (App. Br. 7, 10). However, merely recognizing the mechanism for a process which is suggested by the prior art does not alone impart patentability to it. *See In re Woodruff*, 919 F.2d 1575 (Fed. Cir. 1990); *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1351 (Fed. Cir. 2002); *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1373 (Fed. Cir. 2007). Moreover, it is acknowledged in the Specification that manganese chelates had been suggested in the prior for myocardial imaging (FF 12).

Appellants contend that various claim limitations have been ignored, including dosage (App. Br. 7, 9) and administration times (App. Br. 8). We do not agree with Appellants that the Examiner ignored these limitations. To the contrary, the claimed limitations overlap with those in the prior art (FF 19, 20). Appellants have not identified any deficiency in Rocklage '744's disclosure regarding these limitations.

In regard to the dosage limitation, we note that the Specification states that it was "surprising" that lower dosages of a manganese chelate could be utilized (Spec. 3-4); however, the claimed range overlaps with the prior art. It is well-established that even a slight overlap in ranges establishes prima facie obviousness. *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003). In such cases, it must be shown "that the particular range is *critical*, generally by showing that the claimed range achieves unexpected results relative to the prior art range." *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990). Appellants have not provided rebuttal evidence of unexpected results.

Appellants also argue that Rocklage '744 prefers other ions for its contrast agents, not manganese, and thus would have led persons of ordinary skill in the art away from the subject matter of claim 96 (App. Br. 8-9).

A reference teaches away only when a person of ordinary skill, upon examining the reference, would be discouraged from following the path set out in the reference, or would be led in a direction different from the path that was taken by the applicant. *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). In this case, manganese ions are stated by Rocklage '744 to be "suitable" for MRI (FF 4), were suggested in the prior art for myocardial imaging (FF 12), and thus the prior art would not have discouraged persons of ordinary skill in the art from using them. Furthermore, Rocklage '931 states that Mn chelates "are particularly useful as MRI contrast agents because manganese is less toxic than many paramagnetic metal ions" (FF 11; Rocklage '931, at col. 1, ll. 13-16) – thus, providing an additional explicit reason to have used them in the claimed method.

For the foregoing reasons, we affirm the rejection of claim 96. Claims 76, 77, 79-81, 84-86, and 88-93 fall with claim 96 because separate reasons for their patentability were not provided. *See* 37 C.F.R. § 41.37(c)(1)(vii).

OBVIOUSNESS OVER ROCKLAGE '744 AND GOLDENBERG

Claims 77, 78, and 96 stand rejected under 35 U.S.C. § 103(a) as obvious over Rocklage '744 in view of Goldenberg (Ans. 7).

Claim 77 is directed to the method of claim 96 where the "imaging procedure is a gradient echo or echo planar imaging procedure." Claim 78 depends on claim 77 and further requires that the "imaging procedure is an inversion recovery echo planar imaging procedure." The Examiner finds that the inversion recovery echo MRI is well known in the art – as evidenced by Goldenberg –and thus concludes it would have been obvious to use the prior art method as a "useful and an equivalent method" to those described in Rocklage '744 (Ans. 8).

Appellants do not challenge the Examiner's findings (App. Br. 12), but instead argue that Rocklage '744 does not suggest the subject matter of claim 96 (App. Br. 13-14). As we have addressed these arguments already, we affirm the rejections of claims 77, 78, and 96 for the reasons discussed above.

CONCLUSION

We affirm the rejections of claims 76-81, 84-86, 88-93, and 96 over prior art.

TIME PERIOD

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)

AFFIRMED

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